UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,088	07/12/2001	Avi Ashkenazi	P1618P2C31	2756

9157 7590 08/13/2003

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,088	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-46 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-46 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 11 March 2003 (Paper No. 18) has been entered in full. Claims 39-46 and 49 are amended. Claims 47-48 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 39-46 and 49-51 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the declaration at pg 2 of the previous Office Action (Paper No. 12, 03 October 2002) is *withdrawn* in view of the newly submitted Application data sheet (Paper No. 18, 11 March 2003).

2. The objections to the specification at pg 2-3 of the previous Office Action (Paper No. 12, 03 October 2002) are *withdrawn* in view of the amended title and removal of hyperlinks (Paper No. 18, 11 March 2003).

3. The objection to claims 45-49 at pg 3 of the previous Office Action (Paper No. 12, 03 October 2002) is *withdrawn* in view of the amended and cancelled claims (Paper No. 18, 11 March 2003).

4. The rejection of claims 39-51 under 35 U.S.C. § 112, second paragraph at pg 13-14 of the previous Office Action (Paper No. 12, 03 October 2002) is *withdrawn* in view of the amended and cancelled claims (Paper No. 18, 11 March 2003).

Claim Rejections - 35 USC § 101 and 35 USC § 112

5. Claims 39-46 and 49-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection is set forth at pg 3-8 of the previous Office Action (Paper No. 12, 03 October 2002).

Specifically, claims 39-46 and 49-51 are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245), (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245) lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393; wherein the isolated polypeptide is capable of inhibiting protein production in a cultured cell assay. The claims are also directed to an isolated polypeptide comprising the previously mentioned subparts (a), (b), or (c).

Applicant's arguments (Paper No. 18, 11 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the polypeptides claimed in the application have a specific, substantial and credible asserted utility, which are sufficiently described in the specification. Applicant relies on the PDB12 cell inhibition data in support of patentable utility (pg 207, lines 2-18). Applicant argues that Example 70 describes a cell-based assay in which the PRO293 polypeptide has been demonstrated to have the utility to inhibit protein production by PDB12 pancreatic ductal cells using an AlamarBlue™-based cell proliferation assay. Applicant indicates

that the assay described in Example 70 uses fluorescence read-out, allowing one to calculate total cellular protein concentration produced by PDB12 pancreatic ductal cells in the presence and absence of a particular test molecule. Applicant contends that the results of this assay can be considered as a secondary read-out for cell number and are suitable for the assessment of biological effect of a test substance on pancreatic cells. Applicant states that PRO293 and PRO293-like polypeptides are useful drug candidates in the treatment of pancreatic disorders wherein inhibition of protein production is desirable, such as pancreatitis, which is known to be accompanied by ethanol-induced protein secretory alterations and increased intraductal protein precipitation. It is noted that Applicant cited the Utility Examination Guidelines, MPEP § 2107.01, and *Brenner v. Manson*, 383 U.S. 519, 534 (1966).

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, the asserted utility of PDB12 cell inhibition is not specific or substantial. The specification teaches that "a percent decrease in protein production of greater than or equal to 25% as compared to the negative control cells is considered positive" (pg 207, lines 16-17). However, any slight decrease in protein production, which may even result from the normal variations in cell number, would not indicate that PRO293 specifically inhibits protein production in PDB12 pancreatic ductal cells. Relevant literature also teaches that although the AlamarBlue™ assay does not lead to cell death, the AlamarBlue™ dye may show a reversible, time- and concentration-dependent cell growth inhibition (Gloeckner et al. J Immunol Methods 252(1-2): 131-138, 2001; pg 137, ¶ 2; abstract). Gloeckner et al. also disclose that the application of AlamarBlue™ must be optimized for each cell line utilized and experimental set up (pg 137, ¶ 2). Although the specification teaches that PRO293 is positive in

this assay and it is recognized in the art that AlamarBlue™-based assays are used in the art to study cell proliferation and viability, the specification does not disclose any specific resulting cell numbers or percentages, statistical differences, or the number of repetitions for the assay. Without this knowledge, which could not be gleaned from the instant specification, one of ordinary skill in the art at the time the invention was made would not have been able to use the information obtained from this assay in a useful manner. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Furthermore, the specification of the instant application and Applicant's arguments indicate that PRO293 and PRO293-like polypeptides are useful drug candidates in the treatment of pancreatic disorders wherein inhibition of protein production is desirable, such as pancreatitis, which is known to be accompanied by ethanol-induced protein secretory alterations and increased intraductal protein precipitation. This asserted utility is not specific or substantial. The specification does not disclose any disorders which involve protein secretion by the pancreas which are associated with altered levels or forms of the PRO293 polypeptide. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

It is clear from the instant specification that the "PRO293" polypeptide described therein is what is termed an "orphan protein" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this DNA and protein, may be found to have a specific and substantial credible

utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

6. Claims 39-46 and 49-51 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at pg 8 of the previous Office Action (Paper No. 12, 03 October 2002).

Applicant's arguments (Paper No. 18, 11 March 2003), as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that the concerns for 35 USC §112, first paragraph have been addressed in the arguments made for 35 USC §101.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, since Applicant has not provided evidence to demonstrate that the PRO293 polypeptide has a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

7. Furthermore, regarding 35 U.S.C. § 112, first paragraph, claims 39-43 and 50-51 are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245), (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245) lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393; wherein the isolated polypeptide is capable of inhibiting protein production in a cultured cell assay. The claims are also directed to an isolated polypeptide comprising the previously mentioned subparts (a), (b), or (c). This is an enablement rejection. The basis for this rejection is set forth at pg 8-11 of the previous Office Action (Paper No. 12, 03 October 2002).

8. Claims 39-43 and 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. This is a written description rejection. The basis for this rejection is set forth at pg 11-13 of the previous Office Action (Paper No. 12, 03 October 2002).

Applicant's arguments (Paper No. 18, 11 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the claims have been amended to recite a functional limitation, namely "polypeptides capable of inhibiting protein production in a cultured cell assay". Applicant relies on PDB12 cell inhibition data (pg 207, lines 2-18) in support of such enablement. Applicant contends that procedures to identify and isolate variant proteins of SEQ ID NO: 245 that show equivalent results in assays like the PDB12 cell inhibition assay were well known at the effective filing date of the present application. Applicant cites MPEP 2164.01 to emphasize that the in vitro data provided in the cited example and the specification in general, coupled with the knowledge in the art at the time filing of the invention, provides sufficient guidance to the skilled artisan to make and use this invention without undue experimentation. Applicant concludes that the claimed polypeptides have been fully enabled and sufficiently described in the specification.

Applicant's arguments have been fully considered but are not found to be persuasive.

(i) Regarding the enablement rejection, although the specification may disclose general guidance as to what amino acid positions could potentially be altered (pg 66-67), the claims recite a large number of fragments and variants of the PRO293 polypeptide of SEQ ID NO: 245. Undue experimentation would be required of the skilled artisan to generate the infinite number of variants recited in the claims and screen the same for activity. Specifically, the problem of

predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. Certain positions in the amino acid sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one or ordinary skill in the art to determine, without undue experimentation, the positions in the PRO293 protein and DNA which are tolerant to change and the nature and extent of changes that can be made in these positions.

According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". Although the specification of the instant application teaches art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active PRO293 polypeptide derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to generate the infinite number of variants and fragments of the amino acid sequence of SEQ ID NO: 245, as recited in the claims and to screen them for a desired activity. Such trial and error is considered undue.

Proper analysis of the Wands factors was provided in the previous Office Action (Paper No. 12, 03 October 2002). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which embrace a broad class of structural fragments and variants undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(ii) Additionally, regarding written description, Applicant has not provided facts or evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of polypeptides recited in the claims. The description of one PRO293 polynucleotide and polypeptide in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all mutants, derivatives, and fragments having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245), (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245) lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393. The specification of the instant application and the claims do not indicate what

distinguishing structural attributes are shared by PRO293 and its variants. The specification and claims do not indicate a correlation between protein structure and function. For example, it is not clear what positions in the PRO293 polypeptide sequence are required for function. The specification also does not teach any functional characteristics of the PRO293 polypeptide of SEQ ID NO: 245 because there is no disclosure of any specific resulting cell numbers or percentages, statistical differences, or number of repetitions for the AlamarBlue™ assay.

Furthermore, the broad brush discussion of making or screening for variants and fragments does not constitute a disclosure of a representative number of members. No such fragments were made or shown to have activity. Only one member, PRO293 of SEQ ID NO: 245, is disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed derivatives.

Therefore, only an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 245, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
August 6, 2003

LORRAINE SPECTOR
PRIMARY EXAMINER